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**From:** Spivack, Phyllis  
**Sent:** Thursday, June 26, 2003 7:17 PM  
**To:** STIC-ILL  
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Please obtain for S.N. 10/035100:

Glick et al., "Psychopharmacologic treatment strategies for depression, bipolar disorder and schizophrenia", **Ann. Internal Medicin**, (134, No. 1, 47-60) (2001). **I need the exact date of publication.**

Von Degner et al., "New antidepressant drugs: spectrum and clinical relevance of side effects", **Muench. Med. Wochenschr.** (142, No. 49-50, 35-40) (2000).

Zanni et al., "Combined treatment with reboxetine and antipsychotic drugs on amphetamine-induced locomotion and striatal fos expression", **Society for Neuroscience Abstracts**, Vol. 27, No. 2, pp. 2586 (2001). **I need the exact dat**.

Thank you.

Phyllis Spivack  
1614  
308-4703

V  
8/21/01

## PSYCHIATRIC DISORDERS: SCHIZOPHRENIA—STUDIES OF OTHER COMPOUNDS

## 973.1

**COMBINED TREATMENT WITH REBOXETINE AND ANTIPSYCHOTIC DRUGS ON AMPHETAMINE-INDUCED LOCOMOTION AND STRIATAL FOS EXPRESSION.** M. Zanni<sup>1\*</sup>, A. Giuliani<sup>2</sup>, A. Battaglia<sup>3</sup>, L. Calza<sup>2</sup> and L. Giardino<sup>2</sup>. *1. Pathophysiology Center NS, Hesperia Hosp, Modena, Italy, 2. University of Bologna, Bologna, Italy, 3. Medical Dep., Pharmacia Corp., Milano, Italy.* Combining antidepressant and antipsychotic drugs may be a strategy to improve therapeutic effects on negative symptoms in schizophrenic patients. Moreover, there is recognition that the cognitive symptoms of schizophrenia have the most substantial impact on illness outcome. The involvement of noradrenergic functions in the cognitive impairment associated with schizophrenia has not been as intensively considered. In this study we have investigated the effect of chronic treatment with the selective noradrenaline reuptake inhibitor reboxetine (10mg/kg, s.c., 28 days), alone, and combined to the atypical antipsychotic drug clozapine (30mg/kg, s.c., 28 days) on behavioral tests and genomic (fos and jun) parameters in adult male rats (Sprague-Dawley strain). Reboxetine treatment reduces spontaneous activity in new environment compared to control animals. Increase in locomotion induced by acute amphetamine (1mg/kg, ip) is also lower in reboxetine-treated rats. Clozapine also decreases spontaneous and amphetamine-induced locomotion and combined treatment (clozapine + reboxetine) potentiates this effect. We then investigated fos and jun mRNA expression in prefrontal cortex after acute amphetamine administration in reboxetine, clozapine, and reboxetine+clozapine-treated rats. Both treatments are effective in preventing amphetamine-induced up-regulation of fos and jun mRNA in prefrontal cortex. This study support the rationale in using selective noradrenaline-uptake inhibitors as an adjunct to conventional antipsychotic treatment of schizophrenia. *Supported by Pharmacia Corp., Milano, Italy.*

## 973.3

**THE ADENOSINE A<sub>1</sub> RECEPTOR AGONIST CPA BLOCKS THE ACUTE LOCOMOTOR ACTIVATING EFFECT OF PCP WITHOUT ALTERING PCP-INDUCED SENSITIZATION.** T.L. Sills<sup>1\*</sup>, D.L. Slipoy<sup>2</sup> and P.J. Fletcher<sup>2</sup>. *1. Clinical Res, Boehringer Ingelheim Canada Ltd., Burlington, ON, Canada, 2. CAMH, Toronto, ON, Canada.* The NMDA receptor antagonist phencyclidine (PCP) stimulates locomotor activity when administered acutely and induces sensitization following repeated treatments. In the present study, we assessed the ability of the selective adenosine A<sub>1</sub> agonist CPA to block both the acute locomotor stimulating effect of PCP and the sensitized response following repeated treatments with PCP. On each of five consecutive days male Wistar rats were treated with either saline or 0.5 mg/kg CPA 30 minutes prior to treatment with either saline or 4.0 mg/kg PCP, and locomotor activity was monitored for two hours. Two days following the last of the five days of treatment, all rats were challenged with 2 mg/kg PCP and locomotor activity was monitored for three hours. Results show that acute PCP treatment stimulated locomotor activity and this response was enhanced following repeated treatments. CPA blocked the acute locomotor stimulating effect of PCP, particularly within the first 90 minutes following PCP treatment. CPA did not prevent the development of sensitization to PCP, as substantial enhancement in locomotor activity was observed in animals treated with CPA+PCP, particularly in the last hour of the two hour test sessions. Furthermore, CPA did not prevent the expression of PCP-induced sensitization as assessed with the challenge test. Finally, CPA by itself reduced spontaneous locomotor activity. *Supported by CIHR.*

## 973.5

**TANOSPIRONE, A SEROTONIN-5-HT1A AGONIST, ADDED TO NEUROLEPTIC TREATMENT ENHANCES COGNITIVE PERFORMANCE IN SCHIZOPHRENIA.** T. Sumiyoshi<sup>1,3\*</sup>, M. Matsui<sup>2</sup>, S. Nohara<sup>1</sup>, I. Yamashita<sup>1</sup>, M. Kurachi<sup>1</sup>, C. Sumiyoshi<sup>1</sup>, K. Jayathilake<sup>3</sup> and H.Y. Meltzer<sup>3</sup>. *1. Departments of Neuropsychiatry, 2. Psychology, Toyama Medical and Pharmaceutical University, Toyama, Japan, 3. Department of Psychiatry, Vanderbilt University, Nashville, TN, USA.* We previously reported that the addition of a serotonin-5-HT1A agonist tanospirone to ongoing treatment with typical antipsychotic drugs for 4 weeks improved verbal memory in patients with schizophrenia (Soc Neurosci Abstr 26(1):274; 2000, Biol Psychiatry 49:861; 2001). The purpose of the present study was to evaluate the effects of the adjunctive treatment on two cognitive domains that are relevant to functional outcome in patients with schizophrenia. Twenty-six patients were randomly assigned to adjunctive treatment with 30 mg/day of tanospirone or placebo for 6 weeks. Executive function, measured by the Wisconsin Card Sorting Test (WCST), and secondary verbal memory, measured by the Wechsler Memory Scale-Revised, as well as psychopathology were assessed at baseline and after 6 weeks. Executive function, as indicated by WCST-Categories, and verbal memory improved significantly in the patients who received tanospirone while the control subjects showed no change. There was no significant change in psychopathology ratings in either group. The effectiveness of 5-HT1A agonists for ameliorating cognitive impairment is consistent with the 5-HT1A partial agonist properties of several atypical antipsychotics, including clozapine, quetiapine and ziprasidone. The results suggest the usefulness of 5-HT1A agonists for enhancing social and work function in patients with schizophrenia who continue to receive typical antipsychotic drugs. *Supported by The Japan Research Foundation for Clinical Pharmacology and NARSAD.*

## 973.2

**REBOXETINE ENHANCES DOPAMINE OUTPUT IN THE MEDIAL PREFRONTAL CORTEX OF THE RAT AND POTENTIATES THE ANTIPSYCHOTIC-LIKE EFFECT OF RACLOPRIDE.** I. Linner<sup>1\*</sup>, C. Wiker<sup>1</sup>, M.L. Wadenberg<sup>1</sup>, M. Schalling<sup>1</sup> and T.H. Svensson<sup>1</sup>. *1. Section of Neuropsychopharmacology, Dept. of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.* Central effects of the selective noradrenaline reuptake inhibitor reboxetine related to the mesolimbocortical dopamine (DA) system show principal similarities with those induced by the α<sub>2</sub>-adrenoceptor antagonist idazoxan. Recently we have shown that the suppressant effect of the selective D<sub>2</sub>-receptor antagonist raclopride on conditioned avoidance response (CAR), a preclinical test of antipsychotic efficacy with high predictive validity, is markedly potentiated by the addition of idazoxan. Here we therefore investigated whether also pretreatment with reboxetine may augment the suppressant effect on CAR by raclopride. As a test for the potential extrapyramidal side effect liability of the drug combination, assessments of catalepsy were performed. In addition, the effect of the drug combination on DA output in the prefrontal cortex was assessed by means of microdialysis. Reboxetine (6 mg/kg i.p.) significantly potentiated the CAR suppressant effect of raclopride (0.1 mg/kg s.c.) without affecting catalepsy. Raclopride (0.1 mg/kg s.c.) significantly enhanced the reboxetine (6 mg/kg i.p.) induced, selective increase in prefrontal DA output without having any effect alone. These data show that reboxetine, in similarity with idazoxan, enhances prefrontal DA output as well as the antipsychotic-like effect of raclopride, yet without increasing catalepsy scores. Since clinical studies show augmentation of the antipsychotic effect of classical neuroleptics by idazoxan, it follows that reboxetine may as well provide such augmentation. *Supported by The Swedish Medical Research Council (grant no. 4747) and a grant from The Pharmacia Corp., Kalamazoo, MI.*

## 973.4

**MUSCIMOL PREVENTS NMDA ANTAGONIST NEUROTOXICITY BY ACTING AT GABAERGIC RECEPTORS IN THE DIAGONAL BAND AND ANTERIOR THALAMUS.** X. Jiang<sup>1</sup>, K. Dikranian<sup>1</sup> and N.B. Farber<sup>1</sup>. *1. Psychiatry, Washington University, St. Louis, MO, USA.* Antagonists of the NMDA glutamate (glu) receptor, including phencyclidine (PCP), ketamine and MK-801, have neuroprotective properties in acute brain injury conditions such as stroke and trauma. Unfortunately these agents injure neurons in the retrosplenial cortex (RSC) in rats and produce a schizophrenia-like psychosis in humans. A better understanding of the mechanism underlying these adverse effects should allow for the safer use of these agents and might clarify mechanisms underlying psychosis. We have proposed that the neurotoxic action of NMDA antagonists (NA) is mediated by a complex disinhibition mechanism in which NA abolish GABAergic inhibition, resulting in the simultaneous excessive release of two neurotransmitters at receptors located on vulnerable RSC neurons (acetylcholine at m<sub>3</sub> muscarinic receptors and glutamate at non-NMDA glu receptors). GABAergic agents, when given systemically, prevent NMDA antagonist neurotoxicity. To determine where in brain these agents are working, we injected the GABAergic agonist, muscimol, into different brain regions of rats treated systemically with a neurotoxic dose of MK-801. Muscimol dose dependently prevented MK-801 neurotoxicity when injected into either the diagonal band region of the basal forebrain or the anterior nucleus of the thalamus. We propose that cholinergic neurons in the diagonal band have GABAergic receptors and are the source of the cholinergic input to the injured RSC neurons. In addition we propose that glutamatergic neurons in the anterior thalamus have GABAergic receptors and are the source of the glutamatergic input to the injured RSC neurons. *Supported by AG11355.*

## 973.6

**ATYPICAL ANTIPSYCHOTIC-LIKE PROFILE OF POTENT AND SELECTIVE 5-HT2A INVERSE AGONISTS.** K.E. Vanover<sup>1\*</sup>, C.M. Andersson<sup>1</sup>, E.I. Hansen<sup>1</sup>, S. Harvey<sup>1</sup>, D.T. Hubbard<sup>1</sup>, M.A. Rodriguez<sup>1</sup>, I. Veinbergs<sup>1</sup>, D.M. Weiner<sup>1</sup>, R.E. Davis<sup>1</sup>, M.R. Brann<sup>1</sup> and U. Hacksell<sup>1</sup>. *1. ACADIA Pharmaceuticals, San Diego, CA, USA.* Using a high throughput functional screening approach, we have identified novel compounds as potent 5-HT2A receptor inverse agonists with selectivity compared to other 5-HT2 and monoaminergic receptors. In order to determine their potential use in the treatment of schizophrenia and related disorders, multiple 5-HT2A inverse agonists were compared to clinically active atypical and neuroleptic antipsychotic drugs in a variety of behavioral assays in male mice. The compounds were tested for their ability to attenuate DOI-induced head twitches and dizocilpine- and amphetamine-induced hyperactivity. Further, neuroleptic-like side effects, including catalepsy and cognitive deficits, were evaluated. A prototype 5-HT2A inverse agonist, AC-90179 (1 - 10 mg/kg s.c.), and structurally related analogues attenuated DOI-induced head twitches and dizocilpine-induced but not amphetamine-induced hyperactivity. Catalepsy, cognitive deficits and decreases in spontaneous locomotor activity either did not occur or only occurred at relatively high doses (e.g., 30 mg/kg s.c.). These results suggest that 5-HT2A inverse agonists exhibit an atypical antipsychotic-like profile in mice and a structural series has been identified with oral activity that may represent potential novel treatment for schizophrenia.

**Westfall, Gary**

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**From:** [REDACTED]@acponline.org  
**Sent:** Wednesday, July 02, 2003 11:01 AM  
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**Subject:** date of publication

Dear Mr. Westfall,

the Exact Date  
Of Publication of

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Vol 134 No. 1 Pages 47-60, 2001

Glick et al. "Psychopharmacological Treatment Strategies For Depression,  
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